REMARKS

This Amendment, filed in reply to the Office Action dated September 16, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

As of the Non-Final Office Action dated September 16, 2010, claims 1-5 and 8-18 were all the claims pending in the application and all were rejected.

With this response, claim 1 is amended herewith to incorporate partially the subject matter of Claim 9 therein, and to improve clarity and conciseness. Claims 2, 5, 8, 9 and 18 are canceled herewith without prejudice or disclaimer. Claims 3, 4 and 10-17 are as previously presented.

Exemplary support for the claimed pharmaceutical composition comprising DMSO of currently amended claim 1 can be found in original claim 8 which required that the strontium compound be administered "with a skin penetration enhancing agent" and original claim 9 which required "wherein said skin penetration enhancing agent is dimethylsulphoxide."

Exemplary support for the claimed pharmaceutical composition comprising glycofurol of currently amended claim 1 can be found in Example 18 which states:

"EXAMPLE 18

Skin Penetration Composition

[0057] A strontium-containing composition was prepared by dissolving 40 g strontium chloride hexahydrate in 1000 ml solvent. The composition of the solvent was:

[0058] 50% (volume) distilled water

[0059] 25% (volume) Tetraglycol.RTM. (glycofurol)

[0060] 25% (volume) DMSO"

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Amendment to the Specification

The specification is amended herewith to correct a typographical error in Example 18 on page 18 of the specification as filed. The Applicant kindly requests that the term "glucofural" be replaced with the correctly spelt term "glycofural."

Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 8-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hahn et al. (U.S. Pat. No. 5,804, 203) in view of U.S. Pat. No. 5,866,168, Denhem et al., Remington's, Hahn (2000), Decaris et al., Lambert et al., Knudsen and Parwaresch et al.

According to the Examiner, these publications allegedly teach the following:

(1) the Hahn '203 patent discloses that skin conditions such as psoriasis produce an intrinsic skin irritation and that strontium is effective in suppressing skin irritation and associated tissue inflammation.

(2) the de Lacharrière '168 patent discloses that strontium is a substance P antagonist and is effective in the treatment of pain and inflammatory diseases.

(3) Denhem et al. discloses that radiation therapy causes inflammation of skin tissues.

(4) Remington's discloses that dimethyl sulfoxide is a permeation enhancer.

(5) Hahn (2000) discloses that strontium salts suppress both sensory irritation and inflammation, including neurogenic inflammation.

(6) Decaris et al. disclose that substance P is a well known mediator of neurogenic inflammation.

(7) Lambert et al. disclose that rheumatoid arthritis is an autoimmune disease characterized by inflammation of the synovial membrane of multiple joints and that substance P has proinflammatory properties.

(8) Knudsen discloses that mast cells contain potent mediators of inflammation and that stimulation of the mast cell activates the Na+/K(+)-pump which results in release of histamine from the mast cell. Pump activity is inhibited by strontium ions.

(9) Parwaresch et al. disclose that mast cells are regular constituents of soft tissue and occur with varying frequency in nearly every organ.

According to the Examiner, the Hahn '203 patent discloses the use of strontium to treat inflammation. The difference between Hahn et al. and the claimed invention is allegedly that Hahn et al. does not expressly disclose the treatment of inflammation with strontium, the use of dimethylsulphoxide (DMSO) as a permeation enhancer and the treatment of inflammation associated with radiation therapy or arthritis.

The Examiner alleges the prior art amply suggests that strontium is effective in treating irritation where one of the causes of irritation includes tissue inflammation. Hence, a person of ordinary skill in the art would have allegedly been motivated to modify the prior art with the expectation that strontium would be effective in treating various inflammatory conditions, that DMSO would increase the bioavailability of the strontium and that strontium would be effective in inhibiting inflammation sub-dermally and in soft tissues due to it inhibitory effects on the sodium/potassium pump of mast cells thereby inhibiting secretion of histamine from mast cells.

The Examiner then asserts the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

The Applicants respectfully disagree with the Examiner for the following reasons.

To support an obviousness rejection, MPEP §2143.03 requires "all words of a claim to be considered" and MPEP § 2141.02 requires consideration of the "[claimed] invention and prior art as a whole." Further, the Board of Patent Appeals and Interferences confirmed that a proper, post - KSR obviousness determination still requires the Office make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." In re Wada and Murphy, Appeal 2007 - 3733, citing In re Ochiai, 71 F.3d 1565, 1572 (Fed. Cir. 1995) and CFMT v. Yieldup Intern. Corp., 349 F.3d 1333, 1342 (Fed. Cir. 2003).

In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of **all** of the claim elements.

Claim 1 of the present Application requires:

> 1. (currently amended): **A method of treatment** of a human or non-human animal subject to combat inflammation arising from a condition associated with or without pain wherein **the inflammation is sub-dermal and in soft tissue**, said method comprising topically administering to said subject **an anti-inflammatory pharmaceutical composition comprising a physiologically tolerable strontium compound, a physiologically tolerable carrier, dimethylsulphoxide, and glycofurol.**

Currently amended claim 1 therefore requires at least the following claim limitations:

- A method of treatment of inflammation that is ***sub-dermal*** and in soft tissue, and
- an anti-inflammatory pharmaceutical composition comprising a physiologically tolerable ***strontium compound***, ***dimethylsulphoxide***, and ***glycofurol***.

The Applicants assert the cited references do not render the claimed invention obvious because the combined teachings of the cited references fail to teach or suggest all of the limitations of claim 1.

A. The cited references fail to teach or suggest the treatment of sub-dermal inflammation with a topically applied strontium pharmaceutical composition

1) The Hahn '203 patent teaches strontium cation is effective in suppressing skin irritation not sub-dermal tissue inflammation.

On page 2 of the Office Action, the Examiner asserts that the '203 Hahn patent teaches the treatment of **skin irritation** with strontium.

Specifically the Examiner states:

". . strontium is effective in suppressing **skin irritation** due to sources such as chemical and environmental exposure or **tissue inflammation**, injury or skin pathology (column 9, lines 13-25 of the Hahn '203 patent)." (Emphasis added)

On page 4 of the Office Action, the Examiner appears to contradict himself by stating:

"**Hahn et al. disclose the use of strontium to treat inflammation**. The difference between Hahn et al. and the claimed invention is that **Hahn el al. does not expressly disclose the treatment of inflammation with strontium**..." (Emphasis added)

The Examiner's statements are misleading. Hahn et al. clearly states strontium is effective in suppressing **skin irritation due to** ...tissue inflammation" **not in suppressing sub-dermal** tissue inflammation itself.

As previously submitted, Hahn et al. is concerned with the use of strontium in methods of reducing skin irritation. This is associated with the **surface** of the skin. Any reference in this document to inflammation is solely in the context of one of the potential causes of skin irritation. Use of strontium to treat irritation on the skin's surface neither discloses nor renders obvious treatment of any underlying mechanism which may give rise to it.

Moreover, Applicants' invention specifically relates to **treatment** of a pre-existing condition, namely sub-dermal inflammation in the soft tissues. In contrast, Hahn et al. is concerned with "reducing" or "inhibiting" skin irritation and thus aims to prevent or minimize the development of a condition.

Indeed, this earlier reference is primarily directed to compositions which include both an irritant ingredient (i.e. a component which is capable of inducing skin irritation, e.g. α-hydroxy acids which are widely used in cosmetics) **and** an anti-irritant amount of strontium (see e.g. claim 1 of Hahn et al.).

The intended function of the strontium is therefore clearly to counteract the potential **irritant** effect of the irritant component.

2) Prior art must be enabling to render a claimed invention obvious

MPEP 2145 states that:

> "[a] conclusion of obviousness requires that the reference(s) relied upon be **enabling in that it put the public in possession of the claimed invention**. *In re Hoeksema*, 399 F.2d 269, 274 (CCPA 1968) (stating that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious."); *In re Kumar* 418 F.3d 1361 (Fed. Cir. 2005) (Federal Circuit stating that to "render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the art to make and use the later invention.... Thus, the relevant

> inquiry is... whether [the cited reference] enabled persons skilled in this art to produce" the later invention.) (Emphasis added)

Applicants assert the de Lacharrière '168 U.S. Patent is not relevant to Applicants' invention. Column 1 of the de Lacharrière '168 U.S. Patent does **not** "disclose that strontium is a substance P antagonist and is effective in the treatment of pain, inflammatory diseases, such as rheumatoid arthritis, psoriasis, acne, etc." This background section to the document merely suggests that substance P may be involved in a whole range of diseases, including *inter alia* inflammatory diseases (such as, for example, rheumatoid arthritis) and skin disorders (such as psoriasis and acne rosacea). Treatment of any of these conditions does **not** teach that strontium is effective in treating any associated sub-dermal inflammation. The '168 U.S. Patent only teaches the use of the compositions for the treatment of and/or alleviation of **pain** associated with certain specifically defined skin disorders, namely zona, postzoster, scalds or burns, demodicidosis, skin ulcers, fibrosis, hypertrophic cicatrisation and acne rosacea (see column 2, lines 35-41 and claim 1). The invention in the '168 U.S. Patent is based on the hypothesis that a substance P antagonist will have an **analgesic** effect.

The de Lacharrière '168 U.S. Patent also states in column 2, lines 1-14:

> "By "substance P antagonist" is intended any compound or species capable of partially, or even completely inhibiting the biological effect of substance P. In particular, ***for a substance to be recognized as a substance P antagonist, it must induce a coherent pharmacological response (including or otherwise its binding to the substance P receptor)***, in particular in one of the following tests:
>
> (a) the antagonist substance must reduce the extravasation of the plasma across the vascular wall induced by capsaicin or by an antidromic nerve stimulation, or, alternatively;
>
> (b) the antagonist substance must cause inhibition of the contraction of the smooth muscles induced by the administration of substance P." (Emphasis added)

Applicants assert the de Lacharrière '168 U.S. Patent is **not** an enabling reference because it does **not** include or reference any scientific evidence to show that strontium is a substance P antagonist. To research the role of strontium as a substance P antagonist, a person of ordinary skill would undoubtedly be expected to search the U.S. National Library of Medicine's Medline database for relevant publications. MEDLINE contains bibliographic citations and author abstracts from about 4,600 biomedical journals published in the United States and 70 other countries. The database contains about 12 million citations dating back to the mid-1960s. A Medline search for articles published from the mid 1960s to present having the keywords "strontium" and "substance P antagonist" returns 0 results. A search for "strontium" and "substance P" returns just 4 results, none of which pertain to strontium being a substance P antagonist.

Hence, a person of ordinary skill at the time of filing of the invention would know there is no credible scientific evidence to show strontium is a substance P antagonist.

3) A person of ordinary skill in the art would not expect strontium to act at a <u>sub-dermal</u> location in the skin

Figure 4 of the Hahn (2000) reference, reproduced below, illustrates the proposed mechanism of action of strontium in the skin.

270 Biochemical Modulation and Skin Reaction: Transdermals, Topicals, Cosmetics

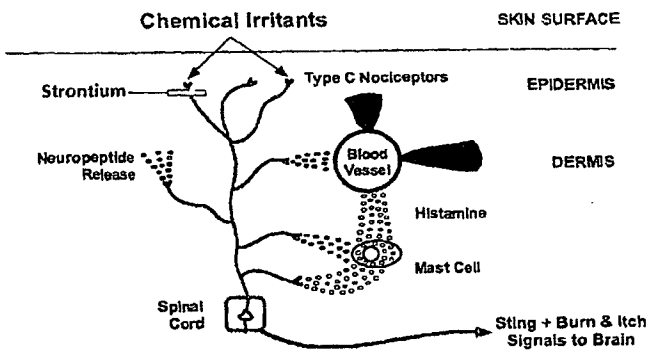


Figure 4 Chemical irritants activate unmyelinated type C nociceptors which trigger a wave of depolarization that synapses in the dorsal root ganglia (DRG) of the spinal cord, and is sensed as sting, bum, or itch. If the stimulation is of sufficient magnitude, intemeurons in the DRG send a retrograde signal down the same C fibers which triggers the release of inflammatory substances including substance P, neurokinin A, calcitonin gene-related peptide (CGRP), and other mediators. These substances trigger vasodilation, and vascular permeability and activate inflammatory cells, including mast cells that, in turn, release another set of inflammatory mediators, including histamine, which further activate nociceptive sensory signals and inflammation.

In relying on this reference the Examiner cites only the passage on page 270 which allegedly suggests topical application of strontium salts "may act to reduce the initial stage of sensory irritation in these conditions as well as the later stage of frank inflammation."

Hahn (2000) is once again primarily concerned with the use of strontium in reducing irritation and erythema arising from the presence of irritating ingredients in topical products. It therefore relates to treatment of **irritation** on the **surface** of the skin. In the studies which are described, a number of chemical irritants which are commonly found in cosmetic and personal care products (e.g. lactic acid, glycolic acid, etc.) are topically applied to the skin both with and without strontium salts in order to assess the ability of strontium to suppress sensory irritation or erythema. The only symptoms of sensory irritation which are recorded are stinging, burning and itching (see under "Sensory Irritation Scale" on page 264). No tests are carried out to determine the potential anti-inflammatory properties of the strontium salts.

a) Type C nociceptors are located only in the dermis

The involvement of type C nociceptors in transmission of stinging, burning, itching, and poorly localized burning pain in the skin is discussed by the Hahn (2000) publication.

Specifically, page 262 of the cited Hahn (2000) reference states:

". . . stinging, burning, itching, and poorly localized burning pain are transmitted by a subset of type C fibers . . . . Also called "nociceptors" (from the Latin nocere, to injure), these neurons are exquisitely sensitive to slight, transient changes in

> their biochemical milieu. . . ***Type C nociceptors are present throughout the dermis and extend to the outermost layer of the viable epidermis***, thus acting as one of the skin's earliest warning systems." (Emphasis added)

b) Neurogenic inflammation is triggered by the Type C nociceptor

Neurogenic inflammation is a process whereby peripheral activation of nociceptors in the upper layers of the skin triggers a central process (in the dorsal root ganglion) which in turn sets up an effect peripherally, namely irritation, erythema or inflammation **at the skin's surface**. Neurogenic inflammation does **not** equate to sub-dermal inflammation, but is simply a process which is associated with the release of certain mediators from the neurons. It is these mediators which drive certain processes, including itching and inflammation **at the skin's surface**.

Specifically, Fig. 4's legend and text on page 262 of the Hahn (2000) review also states:

> "If the magnitude of the irritant stimulus is sufficiently high, interneurons in the DRG or local conduction of depolarizing signals within the terminal arborization of a single nerve fiber send a retrograde depolarization signal down the activated fiber that **triggers the exocytosis of inflammatory mediators at the site of the irritant stimulus**." (Emphasis added)

c) Strontium acts on Type C nociceptors

Page 269 of the Hahn (2000) review states:

> "The fact that strontium can block **irritation** as intense as that produced by 70% unbuffered glycolic acid without causing numbness or other changes in cutaneous sensations suggests that ***strontium is exquisitely selective in its regulation of type C nociceptors (Figure 4)***. In contrast, local anesthetics like lidocaine or procaine not only block irritant sensations, but also block tactile sensations, producing numbness. Recent studies support the concept that ***strontium is highly selective for only nociceptive subsets of sensory neurons*** since strontium nitrate (20%) applied to normal skin did not alter sensory thresholds for cold sensations, warmth sensations, or pain caused by cold or heat."

In his comments on page 270, Hahn merely hypothesizes that neurogenic inflammation may be pathogenically important in irritating and inflammatory conditions, including psoriasis and rheumatoid arthritis. However, these are mentioned simply by way of examples of

conditions or disorders which may have a neurogenic inflammatory component, rather than as targets for treatment using strontium salts. Hahn does not go as far as to suggest that strontium may be used to treat any of these conditions, let alone to treat the underlying inflammation at the **sub-dermal** level.

The Hahn (2000) reference therefore teaches strontium inhibits **skin irritation** by acting on the Type C nociceptors and that neurogenic inflammation caused by skin irritation is triggered by signaling molecules released from these nerves. Neurogenic inflammation caused by skin irritation is therefore **confined** to the epidermis and dermis.

Applicants therefore infer strontium does **not** act on neurogenic inflammation directly. Moreover, the inability of strontium to inhibit the perception of skin irritation but not numbness would also inform a person of ordinary skill that strontium is expected to act on nerves near the surface of the skin **not** at a **sub-dermal** location. Applicant's assertion that strontium can act on sub-dermal inflammation is therefore unexpected and hence unobvious.

4) A person of ordinary skill in the art did not contemplate using strontium for the treatment of sub-dermal inflammation at the time of Applicant's invention

A report in the Internal Medicine News, dated April 15, 2004, entitled "Target: Type C nerve fibers; Strontium May sooth itch without numbness," states:

> "Dr. Hahn noted that physicians have sent correspondence to him suggesting that strontium is effective in suppressing itch caused by poison ivy, nickel allergy, insect bites, lichen planus, Grover's disease, atopic dermatitis, postsurgical scars, sunburn, postherpetic neuralgia, herpes zoster, and traumatic and metabolic neuropathies."

This report published a year after the earliest effective filing date of Applicant's invention, clearly demonstrates a person of ordinary skill in the art such as Dr. Hahn did

not contemplate using strontium for the treatment of sub-dermal inflammation. On the contrary, Dr. Hahn stated:

> "He envisioned three types of uses: pretreatment of skin before exposure to potentially irritating medications or anti-aging treatments; use in conjunction with irritating ingredients; and treatment of skin after exposure to an allergen or other irritant."

5) Inhibition of the Na+K+ ATPase has no significant effect on the histamine release from human cutaneous mast cells

The Examiner cites to Knudsen in an attempt to show "mast cells contain potent mediators of inflammation which release is mediated by the sodium/potassium pump which pump activation is inhibited by strontium ions."

This experimental data is discredited in a 2007 publication by Senol, Ozerol, Patel and Skoner that states:

> "There are controversial reports on the effect of sodium-potassium adenosine triphosphatase (Na+-K+ ATPase) inhibition on mast cell mediator release. Some of them have indicated that ouabain (strophanthin G), a specific Na+-K+ ATPase inhibitor, inhibited the release, whereas the others have shown that ouabain had no effect or even had a stimulatory effect on the mediator secretion. Most of these studies have utilized animal-derived mast cells."
>
> The authors then report:
>
> "RESULTS: The results indicated that ouabain had no significant effect on the non-immunologic histamine release from human skin mast cells, in vitro.
>
> CONCLUSION: ***Na+-K+ ATPase inhibition by ouabain had no significant effect on the non-immunologic histamine release from human cutaneous mast cells and suggested differences between human and animal mast cells.***" (Emphasis added)

Applicants infer from this publication that even if strontium does inhibit the Na/K pump in mast cells it would not prevent histamine release by mast cells and would therefore not have or be expected to have any inhibitory effect on inflammation.

6) *Conclusion*

The Hahn '203 patent teaches strontium cation is effective in suppressing **skin irritation not sub-dermal** tissue inflammation.

The de Lacharrière '168 patent is **not enabling** and fails to show strontium is a substance P antagonist as alleged by the Examiner. A person of ordinary skill would know from Medline searches that there is no credible scientific evidence to show strontium is a substance P antagonist.

The Hahn (2000) publication cited by the Examiner **teaches away** from Applicant's invention because it describes how strontium acts on Type C nociceptors in the epidermis and dermis of the skin and that **neurogenic inflammation caused by skin irritants is confined to dermal not a sub-dermal location** as required by Applicant's claimed invention. Applicant's assertion that strontium acts on sub-dermal inflammation is therefore unexpected and hence non obvious.

The 2007 Senol, Ozerol, Patel and Skoner reference shows that the **inhibition of Na+ K+ ATPase has no significant effect on the histamine release from human cutaneous mast cells**. Hence, the inhibition of the Na/K pump by strontium reported in the Knudsen reference would have no effect on mast cell histamine release and consequently would not be expected to have any effect on sub-dermal inflammation.

The Denhem et al., Remington, Decaris et al., Lambert et al. and Parwaresch et al. references are irrelevant to this analysis because none of them, either alone or in combination, teach, suggest or would motivate a person of ordinary skill in the art to use strontium for the treatment of **sub-dermal** inflammation

Finally, a news report dated one year after Applicant's earliest effective filing date clearly demonstrates Dr. Hahn, an authority in the field, did not himself contemplate using strontium for anything other than the treatment of **skin irritation**.

Applicants therefore conclude the cited references either individually and or in combination fail to teach or suggest treatment of sub-dermal inflammation with a pharmaceutical composition comprising strontium.

B. The cited references fail to teach or suggest an anti-inflammatory pharmaceutical composition comprising a physiologically tolerable strontium compound, a physiologically tolerable carrier, dimethylsulphoxide, and glycofurol.

Topical formulations comprising strontium in combination with DMSO and glycofurol are not disclosed in any of the cited prior art documents. Nor is their use in combating **sub-dermal** inflammation disclosed or suggested.

Glycofurol (tetrahydrofurfuryl polyethylene glycol) is not well known in the pharmaceutical field for providing skin penetration action. Glycofurol is known as a solvent for drugs with solubility problems; this teaches away from its use with the claimed, highly water-soluble, strontium compounds.

Applicants assert it is surprising and unexpected that the positively charged strontium ions are able to penetrate the skin to **sub-dermal** levels in the presence of DMSO and glycofurol. The expectation of those skilled in the art would be that the strontium ion immediately after entering the skin would be bound to negatively charged groups on proteins which form the major constituents of the organic molecules present in any tissue. As a result, it would be expected that these would be unable to penetrate into the sub-dermal tissues and exert a biological effect.

None of the remaining documents provides the missing features of the claimed invention, in particular the **sub-dermal** effect of strontium in combating inflammation and the combination

of DMSO and glycofurol which, surprisingly, has been found to be effective in enhancing delivery of strontium to the sub-dermal tissues.

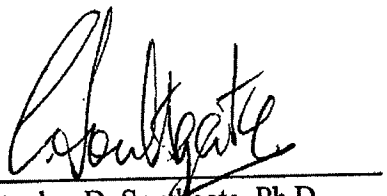
Applicants therefore respectfully request that the rejection of the claimed invention under 35 U.S.C §103 be withdrawn.

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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